IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

BIOGEN INTERNATIONAL GMBH and BIOGEN MA INC.,	
Plaintiffs,	**C.A. No. 17-823-LPS (Consolidated)**
v.	
AMNEAL PHARMACEUTICALS LLC, et. al,	
Defendants.	

BIOGEN'S RESPONSIVE BRIEF ON VALIDITY OF THE '514 PATENT

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MS	Multiple sclerosis
’514 patent	U.S. Patent No. 8,399,514
DMF	Dimethyl fumarate
Nilsson	International Patent Application Publication No. WO 2006/037342
ICH	International Conference on Harmonization
RFF	Biogen’s Responsive Post-Trial Proposed Findings of Fact
DFF	Defendants’ Opening Post-Trial Proposed Findings of Fact
DTX	Defendants’ Trial Exhibit

I. INTRODUCTION

Pursuant to D.I. 349, Biogen submits this brief and proposed findings of fact in response to Defendants' opening brief on alleged invalidity of the '514 patent.

The '514 patent specification describes the claimed invention, disclosing and linking the three elements of the invention set forth in each of the asserted claims: (1) a method of treating MS (2) with DMF and/or MMF (3) at a dose of 480 mg per day. The specification focuses on MS from beginning to end as the disease targeted for treatment. The specification describes methods of treating MS using DMF and/or MMF. Finally, the specification discloses using DMF and/or MMF in an amount of 480 mg/day, identifying this dose as the lowest dose in the narrowest, most preferred range of disclosed doses and connecting it to the known effective dose of 720 mg/day. Accordingly, skilled artisans reading the '514 patent specification in 2007 would have understood that Dr. O'Neill possessed the claimed method of treating MS with a 480 mg/day dose of DMF and/or MMF.

Defendants' arguments to the contrary lack merit and disregard controlling caselaw. A patent may describe multiple inventions but claim only one of them. Similarly, the Federal Circuit has repeatedly stated that a patent need not disclose experimental data, such as clinical test results, to satisfy the written description requirement.

The undisputed evidence also refutes Defendants' inventorship and derivation challenge. By early 2004, Dr. O'Neill had conceived of treating MS patients with 480 mg/day of DMF. Contemporaneous documents and the consistent testimony of multiple credible witnesses amply corroborated his conception and his steadfast belief that 480 mg/day of DMF would effectively treat MS. Defendants did not proffer a prior conception by anyone else, a necessary predicate for a valid derivation challenge.

As to obviousness, the Patent Office issued a Final Written Decision on February 5, 2020 in an *inter partes* review ("IPR") proceeding confirming the patentability of claims 1-20 of the '514 patent. The Patent Office decides patentability in IPRs using the lower preponderance of the evidence burden of proof. This was the second time that the Patent Office has issued a Final Written Decision confirming the patentability of the '514 patent (D.I. 354-1) applying the lower standard.[1] In upholding patentability, the Patent Office considered the same references asserted in this case and further credited Biogen's "strong evidence of unexpected results" D.I. 354-1 at 36-45. Defendants cannot meet the higher clear and convincing evidence burden of proof here.

The Defendants have failed in all respects to establish obviousness. Defendants have failed to establish a *prima facie* case of obviousness based on the asserted references. Even if all of the asserted references were prior art, which they are not, the references describing Biogen's Phase II results do not teach or suggest the claimed invention. Rather, these references would have led skilled artisans away from the claimed invention, motivating them to test DMF doses higher than 720 mg/day to treat MS, given the lackluster efficacy of the 720 mg/day dose in Phase II. Furthermore, as explained in Biogen's opening brief, the objective indicia of non-obviousness, including unexpected results, further compel a holding of validity. (*See* D.I. 352.)

Additionally, the '514 patent is not anticipated. The Defendants' anticipation defense is precluded as a matter of law because the Federal Circuit has held that Nilsson does not disclose treatment of MS with 480 mg/day of DMF. Nilsson's broad disclosure recites a wide range of compounds, diseases and doses, without any preferences, and thus does not teach or disclose the claimed invention.

[1] The Final Written Decision in IPR2018-01403, dated February 5, 2020, was submitted to the Court by letter on February 6, 2020. (D.I. 354.) The prior Final Written Decision is DTX345 (Final Written Decision, IPR2015-01993).

II. DEFENDANTS BEAR THE BURDEN OF PROVING INVALIDITY BY CLEAR AND CONVINCING EVIDENCE

Defendants must prove invalidity by clear and convincing evidence, and that burden remains on them at all times. *See* Biogen Opening ("Op.") Brief at 3. This heavy burden comes with the added burden in this case that the '514 patent claims have been repeatedly reviewed by the Patent Office and found to be patentable. By citing art that was considered or is cumulative of that considered during prosecution and the two IPRs, "Defendants . . . ha[ve] the added burden of overcoming the deference that is due to a qualified government agency presumed to have properly done its job, which includes one or more examiners who are assumed to have some expertise in interpreting the references and to be familiar from their work with the level of skill in the art and whose duty it is to issue only valid patents." *Shire, LLC v. Amneal Pharm., LLC*, 802 F.3d 1301, 1307 (Fed. Cir. 2015) (*quoting PowerOasis, Inc. v. T-Mobile USA Inc.*, 522 F.3d 1299, 1304 (Fed. Cir. 2008)).

This same concept applies to Defendants' written description attack. During prosecution, the Patent Office stated in the context of an obviousness rejection that unexpected results were not in dispute, but the "particular combination" recited in the claimed method was not "described in the specification as filed." (RFF 44-45.) Biogen responded by noting that the specification focuses on treating MS with DMF and describes the use of 480 mg/day DMF, pointing to many of the same "blaze marks" and description on which Dr. Wynn relied on in forming his opinions at trial, after which the Patent Office allowed the claims. (RFF 46-50.) Consequently, although it did not issue a formal rejection under 35 U.S.C. § 112, the Patent Office specifically raised the issue of written description support and then withdrew its stated concern in view of Biogen's identification of the written description support for the claimed method. (RFF 44-50.)

III. DEFENDANTS FAILED TO PROVE BY CLEAR AND CONVINCING EVIDENCE THAT THE INVENTION OF THE '514 PATENT LACKS WRITTEN DESCRIPTION

The evidence at trial demonstrated that skilled artisans reading the '514 patent specification in 2007 would have understood that the inventor of the asserted claims possessed the claimed method of treating MS with a 480 mg/day dose of DMF.[2]

"The written description requirement is met when the disclosure 'allows one skilled in the art to visualize or recognize the identity of the subject matter purportedly described.'" *Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1308 (Fed. Cir. 2015) (quoting *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F.3d 956, 968 (Fed. Cir. 2002)). Written description "is about whether the skilled reader of the patent disclosure can recognize that what was claimed corresponds to what was described; it is not about whether the patentee has proven to the skilled reader that the invention works, or how to make it work.'" *Alcon Research Ltd. v. Barr Labs., Inc.*, 745 F.3d 1180, 1191 (Fed. Cir. 2014). Indeed, there is no requirement that the patent specification must contain "either examples or an actual reduction to practice." *Enzo*, 323 F.3d at 968. Rather, "the test requires an objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art," *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010), to determine whether "the patentee has provided an adequate description that 'in a definite way identifies the claimed invention' in sufficient detail such that a person of ordinary skill would understand that the inventor had made the invention at the time of filing." *Allergan*, 796 F.3d at 1308 (quoting *Ariad*, 598 F.3d at 1352). The '514 patent and its claims meet this standard.

[2] Defendants' experts Drs. Lindsey and Stobbe agreed with Biogen's experts that the definition of a skilled artisan with respect to the '514 patent claims is one having at least a medical degree with at least three years of training in neurology and at least three years of clinical experience in treating MS. (RFF 56-59.)

A. The Specification Demonstrates Possession of the Claimed Invention

The patent discloses and links the three recited elements of the asserted claims: (1) a method of treating MS with (2) DMF and/or MMF (3) at a dose of 480 mg per day.

1. The Specification Describes Treatment of MS

The '514 patent "describe[es] a treatment of multiple sclerosis from the first to the last paragraph of the specification." (Wynn 667:15-17.) The specification begins by discussing in detail the characteristics, prevalence and goals for treatment of MS. (RFF 61, 63, 66.) Its first substantive paragraph highlights MS as the neurological disease for treatment. (RFF 66.) The specification next explains that MS is "characterized by inflammation in parts of the CNS, leading to loss of the myelin sheathing around neuronal axons (demyelination), loss of axons, and the eventual death of neurons, oligodendrocytes and glial cells," which the parties agreed are the characteristics or "hallmarks" of MS. (RFF 66; Yong 103:12-104:17.) Dr. Duddy similarly explained that, consistent with this language, MS is the "classic demyelinating disease." (Duddy 471:13-18.) The specification further discusses the prevalence of MS, the "most common cause of non-traumatic disability in young individuals" (Wynn 605:24-606:6), and goals for treatment as of 2007, namely "reduc[ing] inflammation," [p]romoting CNS remyelination as a repair mechanism and otherwise preventing axonal loss and neuronal death." (RFF 66.)

The specification then describes Methods 1-3 directed to methods of screening for compounds to treat neurological diseases, and Methods 4 and 5 directed to methods for treating neurological diseases. Method 4 relates to the use of at least one compound such as DMF, and Method 5 relates to the use of such a compound in combination therapy. Specifically, column 3, lines 1-9 describe treatment Methods 4 and 5, and lines 10-14 specify that MS is a neurological disease that may be treated with Methods 4 and 5. (RFF 68.) The additional descriptions of treatment Method 4 appearing at column 4, lines 33-37, and column 8, lines 45-47, indicate that

treatment Method 4 can be used to "slow or prevent demyelination, axonal loss and/or neuronal death" the same "hallmarks" of MS described at column 1, lines 15-20, further emphasizing that MS is the neurological disease targeted for treatment by Method 4. (RFF 68.) Indeed, "[m]ultiple sclerosis is mentioned over 30 times in the patent." (Wynn 662:7-8; *see also id.* 616:7; RFF 67.)

In addition, the patent examples also indicate that the specification is focused on MS. Example 3 employs an animal model for MS, the Experimental Autoimmune Encephalomyelitis (EAE) mouse model, which is also explained in detail at column 16, line 67 to column 17, line 38 of the specification. (RFF 69.) As Biogen's Dr. Wynn explained at trial, skilled artisans would have understood by 2007 that the EAE model was the "most widely used" model, specific only to MS, in developing MS therapies. (Wynn 612:23-614:21; RFF 69.)

2. The Specification Describes Treating MS with DMF and/or MMF

The specification further links treating MS with DMF and/or MMF through treatment Method 4. The specification repeatedly highlights only DMF and MMF as examples of compounds for use in Method 4 for treating neurological diseases like MS. This is detailed in each description of treatment in Method 4, appearing at column 3, lines 1-4, column 4, lines 29-33 and column 8, lines 35-38 ("In some embodiments method 4 comprises administering to the mammal a therapeutically effective amount of at least one neuroprotective compound having Formula I, II, III, or IV, e.g., a fumaric acid derivative (e.g., DMF or MMF."). (RFF 70-71.) In the face of this clear and repeated disclosure, Defendants' Dr. Yong conceded that the patent teaches that DMF or MMF can be used to practice Method 4. (Yong 100:16-18; RFF 71.) Thus, Method 4 specifically links the treatment of MS with the administration of DMF and/or MMF. (RFF 70.) The examples similarly disclose experiments using only DMF and/or MMF, further indicating that the specification, including its disclosed treatment methods, are focused on these specific compounds. (RFF 72-74; *e.g.*, (DTX001_0025) '514 patent col. 22:12-13 ("The results [from Example 3],

shown in Figs. 3 and 4, demonstrate MMF and DMF activation of Nrf2 in vivo.").) Accordingly, a POSA would understand that the '514 patent discloses treating MS with DMF and/or MMF. (RFF 75.)

3. The Specification Describes 480 mg/day DMF As An Effective Dose To Treat MS

The '514 patent specification states that "[i]n some embodiments Method 4 comprises administering to the mammal a therapeutically effective amount of at least one neuroprotective compound having Formula I, II, III, or IV, e.g., a fumaric acid derivative (e.g., DMF or MMF)." (DTX001 at 3:29-33.) The specification ties the concept of effectiveness to MS by defining "therapeutically effective dose" and "therapeutically effective amount" with the same language used to characterize MS, i.e., the "hallmarks" of MS. (RFF 76-78; Wynn 663:15-664:8.) As to specific amounts of DMF to be used, the specification states:

> For example, an ***effective dose of DMF*** or MM[F] to be administered to a subject ***orally*** can be from about 0.1 g to 1 g per [d]ay, 200 mg to about 800 mg per day (e.g., from about 240 mg to about 720 mg per day; or from ***about 480 mg to about 720 mg per day***; or about 720 mg per day.

(DTX001 at 18:52-64 (emphasis added).) The specification thus identifies 480 mg/day of DMF by disclosing this dose as the lowest dose in the narrowest range (480-720 mg/day) of effective doses for oral administration. (RFF 78-79.) This narrowest range specifically links the claimed dose of 480 mg/day to 720 mg/day of DMF, and the defendants and all experts agreed that a POSA would have known in 2007 that 720 mg/day of DMF was an effective dose for treating MS. (RFF 78-80.) For example, Biogen's expert Dr. Wynn testified that the excerpt above "links [the POSA] to 480, a dose not previously tested, and directs me towards that dose and links that to the known effective dose of 720 milligrams per day." (Wynn 624:20-22; RFF 78.) And Defendants' Dr. Lindsey agreed that this disclosure teaches "progressively narrowing" dose ranges. (Lindsey

136:8-9; *see* RFF 121.) This paragraph concludes by describing that 720 mg/day, for example, may be orally administered in separate "equal doses," and a skilled artisan would understand that such separate administration applies to the other effective DMF doses, such as 480 mg/day. (DTX001 at 18:63-64; RFF 78, 82.) Dr. Wynn confirmed this understanding in explaining that "the key words in this last sentence of the paragraph are ***for example***. For example, 720 would be given in split doses. When you give 480, one would also give split doses as well." (Wynn 625:20-626:13) (emphasis added). Accordingly, a POSA would understand that this paragraph's concluding sentence is not limited to 720 mg/day, and includes other effective DMF doses, including 480 mg/day.

Ignoring these specific teachings relating to the claimed 480 mg/day dose, Defendants point to more general guidance regarding dose selection to suggest that the patent discloses only a "research plan" and not specific effective doses. (Def. Op. Br. at 5.) The specification, however, specifically identifies effective doses of DMF and/or MMF for oral administration. (RFF 78-80.) The specification further provides detailed guidance with respect to the only variables associated with dosages of DMF or MMF, explaining how to account for the "route of administration, excipient usage, and the possibility of co-usage with other therapeutic treatments including use of other therapeutic agents." (DTX001 at 18:54-58.) The specification describes *orally* administering an "effective dose" of DMF or MMF, thus specifying the route of administration. (*Id.* 18:58-59; RFF 78) and the dosing disclosure excerpted above does not teach co-usage of effective doses of DMF or MMF with other therapeutic treatments. Consequently, co-usage is not a factor that needs to be considered. (*See* DTX001 at 18:58-64; RFF 90.) Moreover, directly following the disclosure of effective doses, including 480 mg/day, the specification provides information on excipients that may be used in practicing the claimed invention and identifies U.S.

Patent No. 6,509,376 ("the '376 patent") describing "formulations containing DMF and/or MMF." (DTX001 at 19:26-27; RFF 82-83.) The '376 patent teaches preparation of "enteric-coated microtablets in capsules" (DTX340 at 6:10-53) —the same formulation Biogen used in its Phase II study that established that 720 mg/day of DMF was effective in treating MS. (RFF 84.) The patent specification thus provides specific and detailed teachings relating to the treatment of MS with the claimed effective dose of DMF.

Finally, the disclosure of "about 480 mg to about 720 mg per day" is a constructive reduction to practice of the claimed 480 mg/day DMF dose. *See Ariad*, 598 F.3d at 1352 ("[T]he written description requirement does not demand either examples or an actual reduction to practice; a constructive reduction to practice that in a definite way identifies the claimed invention can satisfy the written description requirement.").

In this case, the '514 patent specification specifically describes the claimed 480 mg/day dose as the lower endpoint of the most preferred dose range and thus constructively reduced the 480 mg/day dose to practice. *Bigham v. Godtfredsen*, 857 F.2d 1415 (Fed. Cir. 1988), cited by Defendants, involved a patent application that disclosed only one halogen species (chloro). The Federal Circuit held that the disclosure of this species did not serve as a constructive reduction to practice of two other undisclosed halogen species (bromo and iodo compounds). *Id.* at 1417-18.

B. Dr. Wynn Properly Analyzed the '514 Patent and Found Written-Description Support for the Claimed Invention

A proper written description analysis starts with the claims. *In re Moore*, 439 F.2d 1232, 1235 (C.C.P.A. 1971) ("[I]t should be realized that when the first paragraph [of 35 U.S.C. § 112] speaks of 'the invention,' it can only be referring to that invention which the applicant wishes to have protected by the patent grant, i.e., the claimed invention. For this reason, ***the claims must be analyzed first*** in order to determine exactly what subject matter they encompass.") (emphasis

added). Accordingly, Biogen's expert Dr. Wynn began his written-description analysis by first explaining the subject matter encompassed by those claims. (RFF 60.) Specifically, he identified the following three elements of each method claim: (1) a method of treating MS (2) with DMF and/or MMF (3) at a dose of 480 mg/day. (Wynn 604:5-8; RFF 62.)

Dr. Wynn, a skilled artisan, then assessed the written description support for each claimed method of treatment by looking within the four corners of the specification. *See Alcon*, 745 F.3d at 1015-16 (The written description "assessment 'requires an objective inquiry into the four corners of the specification'") (quoting *Ariad*, 598 F.3d at 1351). He explained that "[i]f I pull back in my chair as a treating physician reading this patent, a person of skill in the art, I read the patent. The patent directs me, the focus about MS from the very beginning, it describes the methods, methods of screening compounds . . . and methods of treatment, Methods 4 and 5. Now we need to know, well, how much do you give? This [dosing disclosure] is the section that addresses that." (Wynn 668:17-24; *see also id.* 667:9-12; RFF 61.) He thus explained that the specification starts and ends by discussing MS, describes the treatment of MS with DMF and/or MMF in Method 4, and identifies 480 mg/day as an "effective dose" of DMF and/or MMF by reciting it as the low endpoint in the narrowest, most preferred range and connecting it to the known effective dose of 720 mg/day.[3] (RFF 60-62, 64-65, 72, 80; *Ariad*, 598 F.3d at 1351.)[4]

There is no requirement, as Defendants suggest, that the three claim elements must be disclosed in a single paragraph (Def. Op. Br. at 9). "[C]laimed subject matter need not be described

[3] Dr. Wynn therefore did not "work backwards," as Defendants assert. Defendants' own brief begins its written description analysis with the claims. *See* Defendants Op. Br. at 3 ("The asserted claims lack written description. All claims share the combination of three elements: (1) treating MS; (2) with DMF; (3) at 480 mg/day.".)

[4] Defendants mischaracterize Dr. Wynn's testimony in that they quote Defendants' counsel, instead of Dr. Wynn, in describing Dr. Wynn's analysis. *See, e.g.*, D.I. 351 DFF 28-29.

in haec verba in the specification in order for that specification to satisfy the description requirement . . . ." *In re Smith*, 481 F.2d 910, 914 (C.C.P.A. 1973); *see also Vas-Cath*, 935 F.2d at 1563-64. Rather, "the requirement is met if a [POSA] would find it is 'reasonably clear what the invention is and that the patent specification conveys that meaning.'" *Pfizer Inc. v. Teva Pharms. U.S.A., Inc.*, 882 F. Supp. 2d 643, 699-700 (D. Del. 2012) (quoting *All Dental Prodx, L.L.C. v. Advantage Dental Prods., Inc.*, 309 F.3d 774, 779 (Fed. Cir. 2002)). Here, the specification provides a detailed and comprehensive description of the three related elements of the claimed treatment method. *See supra* Section III.A; *see also* Wynn 667:9-12; 668:17-24.

Novozymes A/S v. Dupont Nutrition Biosciences APS, 723 F.3d 1336 (Fed. Cir. 2013) does not assist Defendants. In *Novozymes*, the patent claimed a specific enzyme variant having a substitution at a particular amino acid position and possessing increased thermostability. *Id.* at 1341. The specification, however, "contain[ed] no disclosure of any variant that actually satisfie[d] the claims." *Id.* at 1348. Instead, the specification disclosed 7 parent enzymes of approximately 500 amino acid long enzyme chains, each having 33 target substitution positions, and 40 possible mutations at each target position. *Id.* at 1340. The *Novozymes* Court held that the specification failed to provide sufficient "blaze marks" that would guide one toward the specifically claimed combination among the "slew of competing possibilities." *Id*. at 1349. The court further emphasized that, to satisfy the written description requirement, the application must describe the claimed subject matter "as an integrated whole rather than as a collection of independent limitations." *Id*. In contrast, the '514 specification describes the invention as an integrated whole linked by Method 4 and provides clear blaze marks to all three claimed elements, namely (1) treating MS, a disease target highlighted throughout the specification, (2) with DMF and/or MMF, the only two specific compounds repeatedly called out in the disclosure and

examples, (3) at a dose of 480 mg/day, described as an "effective dose" and disclosed in the narrowest range and connected to a known effective dose for treating MS. *See supra* Section III.A.

Defendants incorrectly suggest that Biogen was required to disclose all aspects of its Phase II study in the '514 patent specification. (*See* Def. Op. Br. at 11-13.) Skilled artisans, however, read a patent with knowledge of the relevant art, and skilled artisans were well aware of all pertinent details of Biogen's Phase II study. *See Capon v. Eshhar*, 418 F.3d 1349, 1357-59 (Fed. Cir 2005) (vacating a finding of lack of written description support that failed "to consider the state of the scientific knowledge" because "[t]he 'written description' requirement must be applied in the context of the particular invention and the state of the knowledge."). Here, ***all experts*** agree that, by 2007, 720 mg/day DMF was a known oral, effective dose in treating MS based on the results of Biogen's Phase II study. (RFF 80.) Accordingly, a POSA with this knowledge would have read the '514 patent as calling out 480 mg/day by connecting it to a known effective dose in the narrowest, most preferred range of doses, 480 to 720 mg/day. *See Capon*, 418 F.3d at 1357. Contrary to Defendants' suggestion, Biogen is not advancing "an obviousness analysis based upon combining disclosures in the patent and the prior art." (Def. Op. Br. at 10 (citing *Ariad*, 598 F.3d at 1352).) Rather, Biogen is simply acknowledging that skilled artisans would have read the patent's disclosure with an understanding of the state of the art.

Finally, the fact that the specification describes unclaimed lower doses of DMF and/or MMF that may be ineffective to treat MS is irrelevant to the determination of whether the specification provides written description support for the claimed 480 mg/day dose of DMF and/or MMF to treat MS. *See Snitzer v. Etzel*, 465 F.2d 899, 902 (C.C.P.A. 1972) ("[W]e fail to see the relevance of the listing of several inoperative species when the species claimed is operative . . . .'").

C. Defendants' "Drug Discovery" Patent Arguments Ignore The Specification's Clear Teachings to the Person Skilled in The Field of the Claimed Invention

An "'invention' is defined by the claims," *Vas-Cath*, 935 F.2d 1555, 1565 (Fed. Cir. 1991), and inventors may describe multiple inventions in a single patent. *See* 35 U.S.C. § 121; 37 C.F.R. §1.41(a).[5] Defendants ignore these fundamental principles by focusing on only certain portions of the '514 patent specification and then alleging that these portions establish that the '514 patent is directed only to "drug discovery." (Def. Op. Br. at 4-6.) Those portions of the specification, however, relate to Dr. Lukashev's screening methods, discussed, for example, in Methods 1-3, which methods are not claimed in the asserted claims of the '514 patent. Rather, the claims of the '514 patent are directed to Dr. O'Neill's inventive method of treating MS with 480 mg/day DMF and/or MMF. *See Cooper Cameron v. Corp. v. Kvaerner Oilfields Prods.*, 291 F.3d 1317 1322-23 (Fed. Cir. 2002) (reaffirming *Vas-Cath*). Consequently, the specification's discussion of Dr. Lukashev's screening methods for use in drug development is irrelevant to, and most certainly does not somehow erase, the disclosure of Dr. O'Neill's claimed invention of treating MS with 480 mg/day DMF and/or MMF. *See supra* Section III.A.

Defendants' reliance on Dr. Yong's "drug discovery" testimony is irrelevant for similar

[5] Amendments to inventorship are appropriate to conform with changes as to what is claimed. 37 C.F.R. §1.41(a). Biogen therefore properly added Dr. O'Neill as an inventor when amending the claims to focus on his method of treating MS. (RFF 41-44.) Defendants' reliance on *Quake v. Lo*, 928 F.3d 1365, 1373 (Fed. Cir. 2019), an interference case, is misplaced. There, the Federal Circuit addressed a situation in which "[c]laims [we]re added later during prosecution in response to development by others . . . . [T]he first time Quake tried to cover [the claimed method] with this specification was after the publication of Lo's patent application directed to [the claimed method]: Quake then canceled all his pending claims and replaced them with claims covering [the claimed method], creating a mismatch between the claims and the originally filed specification." *Id.* There is no allegation here that Biogen has attempted to patent the work of others. Quake created a mismatch because its specification provides "no express description or sufficient blaze marks of the claimed method as a whole" and misses a "key [] disclosure" that "could have provided a supporting blaze mark." *Id.* at 1376, 1378. In contrast, the '514 patent describes each of the three claimed elements as a whole with clear blaze marks.

reasons. Moreover, it is uncontested that Dr. Yong is not a clinician and therefore is not one skilled in the relevant art of the claimed invention directed to methods of treating MS.[6] (RFF 53, 56, 59.) In addition to ignoring the subject matter actually claimed in the patent, Dr. Yong also never considered the background, education and deposition testimony of Dr. O'Neill, the inventor of the claimed method of treating MS with 480 mg/day DMF. (RFF 59; 96:14-16 (Q: "[Y]ou did not review the deposition transcript of inventor O'Neill; is that correct? A: That's correct."); *see also id.* 94:15-18.) Instead, Dr. Yong focused exclusively on the contributions and testimony of Dr. Lukashev—also not a POSA in the field of the claimed invention—in forming his opinions in this case. (Yong 94:2-96:20; RFF 59.) This is not surprising given Dr. Yong's admission that he had been "asked to look at the specification as relates to the science of the discovery." (Yong 99:7-9.) Accordingly, the Court should disregard Dr. Yong's "drug discovery" testimony both because he is not a POSA and it is irrelevant to the claimed methods of treating MS.

Gen. Hosp. Corp. v. Sienna Biopharms., Inc., 888 F.3d 1368 (Fed. Cir. 2018), cited by Defendants, does not support their "drug discovery" theory. In *Sienna*, the patent specification disclosed a "range of concentrations" and "discrete values within that range, none of which [were] the claimed value." *Id.* at 1372. Unlike in *Sienna*, the '514 patent specifically recites the claimed 480 mg/day dose and identifies it as an "effective dose" by including it as the lower endpoint in the narrowest range that connects this 480 mg/day dose to the known effective dose of 720 mg/day. (RFF 65, 78.)

[6] While Biogen's experts and Defendants' experts Dr. Lindsey and Dr. Stobbe agreed on a definition for a POSA, Dr. Yong advanced an alternative definition based on certain portions of the patent specification. However, "[i]t is the person of ordinary skill ***in the field of the invention*** through whose eyes the claims are construed." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005) (quoting *Multiform Desiccants, Inc. v. Medzam, Ltd.*, 133 F.3d 1473, 1477 (Fed. Cir. 1998)) (emphasis added).

D. Defendants Improperly Conflate Obviousness and Written Description

Defendants improperly inject non-obviousness principles into the written description analysis, misinterpret *Nuvo Pharms. v. Dr. Reddy's*, 923 F.3d 1368 (Fed. Cir. 2019), and mischaracterize the testimony of Biogen's witnesses and Biogen's arguments during prosecution. (*See* Def. Op. Br. at 11-13.)

Obviousness and written description are separate inquiries based on distinct analyses of different types of evidence. *Compare* 35 U.S.C. § 103 ("[T]he differences between the claimed invention and the ***prior art*** . . . .") *with* 35 U.S.C. § 112 ("The ***specification*** shall contain a written description of the invention. . . .") (emphasis added). Obviousness determinations, including whether the invention demonstrates unexpected properties compared to the prior art, are not based on a patent specification's disclosure. *See Graham v. John Deere Co.*, 383 US 1, 17-18 (1966). Written description, on the other hand, is based on the specification's disclosure and how it would be understood by one of ordinary skill in the art. *See Ariad*, 598 F.3d at 1351 ("[T]he test for sufficiency is whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date.").

Defendants point to the unexpected results exhibited in Biogen's Phase III trials to argue that the claimed invention must lack written description. (Def. Op. Br. at 12.) This argument finds no support in the law. Biogen's statements concerning unexpected results, including Dr. Dawson's declaration during prosecution and Drs. Duddy's and Dawson's testimony at trial, were based on what would have been expected based on the state of the art ***before the patent***. (RFF 86-87; Biogen Op. Br. at 4-13.) Such evidence and testimony about what a POSA would have expected ***before*** reading the patent establishes that the '514 patent is directed to a non-obvious invention with unexpected results. *See Allergan*, 796 F.3d at 1306 ("[T]he claimed formulation exhibited

'unexpected results,' which differed in kind, not just in degree, ***from the prior art***.") (emphasis added). In contrast, a proper written description analysis considers what a POSA would understand *after reading the patent*. *Allergan*, 796 F.3d at 1308. In analyzing written description, Biogen's expert Dr. Wynn determined that a POSA would conclude, after reading the patent, that the specification describes the claimed invention. *See* Section V.A.

Defendants also argue, relying on *Nuvo*, that the specification must contain proof that the invention works. (*See* Def. Op. Br. at 12-13.) This argument is contrary to *Nuvo* and the well-settled case law it cites. In *Nuvo*, the Federal Circuit found that the patent claims directly conflicted with the specification. The patent claims in that case required a "therapeutically effective amount of uncoated PPI that can raise the gastric pH to at least 3.5." 923 F.3d at 1379. The *Nuvo* Court concluded that this claim was inconsistent with the specification's teaching that uncoated PPI would undergo "destruction by stomach acid" and thus be unable to raise gastric pH. The court further stated that in the specification "there [was] no alternative disclosure explaining that uncoated PPI could still be effective to raise pH" as was claimed. *Id.* at 1373-74; *see* U.S. Patent No. 6,926,907 at 1:66-2:1, and, consequently, held that "the specification [was] fatally flawed." *Nuvo*, 923 F.3d at 1381.

Implicitly cautioning against the misapplication advanced by Defendants here, the *Nuvo* Court explained that its decision was highly fact-specific and based on the claims and unique specification at issue:

> Written description analyses are ***highly fact specific***. Based on the specific facts of certain cases, ***it is unnecessary to prove that a claimed pharmaceutical compound actually achieves a certain result***. . . . In this case, the inventor chose to claim the therapeutic effectiveness of uncoated PPI, but he did not adequately describe the efficacy of uncoated PPI so as to demonstrate to ordinarily skilled artisans that he possessed and actually invented what he claimed. And the evidence demonstrates that a person of ordinary skill in the

> art reading the specification would not have otherwise recognized, based on the disclosure of a formulation containing uncoated PPI, that it would be efficacious because he or she would not have expected uncoated PPI to raise gastric pH. Under those facts, the patent claims are invalid for lack of adequate written description pursuant to § 112, ¶ 1.

Id. at 1383-84 (emphasis added).

Here, in contrast to *Nuvo*, the '514 patent claims are consistent with the specification. Nothing in the '514 patent cautions against using the claimed 480 mg/day DMF dose or otherwise disparages the results obtained in treating MS with that dose. The '514 patent teaches that 480 mg/day, connected to a known effective dose in treating MS, is an "effective dose" and further defines "therapeutically effective dose" in relation to the "hallmarks" of MS. (RFF 65, 77-80.)

Therefore, based on these facts and consistent with *Nuvo*, the '514 patent specification describes the claimed invention. It is unnecessary, as Defendants suggest, to prove that the claimed dosage achieves efficacy. 923 F.3d at 1383; *see also Allergan*, 796 F.3d at 1309 (holding that experimental data demonstrating effectiveness is not required to support written description).

Defendants argue that testimony and statements of Biogen made during prosecution, that the Phase II studies taught away from the claimed invention, suggest that the claims lack written description support. (Def. Op. Br. at 12 ("[The Phase II] studies would have indicated to a POSA that the claimed invention would not work.").) Defendants again conflate principles of obviousness and written description. Biogen has never argued, nor have any of its witnesses testified, that a skilled artisan would have believed ***after reading the '514 patent*** that "the claimed invention would not work." Rather, Biogen has consistently argued, and the evidence establishes, that a skilled artisan would have believed after reading the patent that 480 mg/day would work given the disclosure that it is an effective dose and the fact that the inventor linked this dose to the 720 mg/day dose that showed statistical significance in the Phase II study. (RFF 86-87.) The

evidence that Defendants point to regarding surprise relates to unexpected results, and in particular to the surprise regarding the unexpected *magnitude* of efficacy seen with 480 mg/day DMF in the Phase III trials. (D.I. 353 FF 11-44; *see* Biogen Op. Br. at 4-13.) Indeed, Dr. Wynn testified, "I was terribly surprised that it was so effective." (RFF 114; Wynn 694:13-14; *see also id.* 718:20-719:3; 719:10-19; 690:10-12; 693: 23-25.) Dr. Duddy similarly explained, "what has been surprising is the magnitude of that efficacy . . . ." (RFF 114; Duddy 488:15-23.)

Finally, in arguing that the asserted claims lack written description, Defendants do not differentiate between claims that recite "therapeutically effective amount" and those that do not. *See* Def. Op. Br. at 3 (focusing on only certain elements of the asserted claims). As to the asserted patent claims that require a "therapeutically effective amount," Defendants' arguments fail for the reasons discussed above. Defendants' arguments are inapplicable, however, to the asserted patent claims that do not include this limitation, and Defendants do not address those claims. Specifically, claim 11 and its dependent claims simply requires a method of treating one in need of MS treatment by "orally administering to the subject about 480 mg per day" of DMF and/or MMF. And for the same reasons that the specification describes claims reciting a "therapeutically effective amount," *see supra* Section III.A., it necessarily describes claim 11 and dependent claims 12-14, which do not include any such language.

E. The '514 Patent is Distinguishable From Nilsson

Defendants claim that Biogen's successful arguments against written description of the claims in Nilsson somehow suggest that the '514 patent lacks written description support. (Def. Op. Br. at 13-15.) Biogen's arguments against Nilsson, which differs substantially from the '514 patent, do not apply here. Nilsson lists a wide-ranging number of conditions for potential treatment, identifies a broad scope of fumaric acid esters of purported use for such treatment and directs one to use a scale-up dosing regimen with a number of indiscriminate dosing ranges through

which one passes on the way to a target dose. (RFF 118, 120-23.) Forward Pharma argued in an interference proceeding that these broad and unconnected disclosures supported its contention that it was entitled to claim the same subject matter set forth in the '514 patent claims. The Patent Office and the Federal Circuit disagreed, holding that Nilsson fails to direct the skilled artisan to any specific dose, any specific active ingredient, or treatment of any specific disease other than psoriasis, and fails to provide any blaze marks linking any of those items such that the skilled artisan would arrive at Dr. O'Neill's invention. *See FWP IP ApS v. Biogen MA, Inc.*, 749 Fed. Appx. 969, 977 (Fed. Cir. 2018); *Biogen MA Inc. v. Forward Pharma A/S*, Pat. Intf. No. 106,023 (Decision, Mar. 31, 2017). In contrast, as explained above, the '514 patent specification focuses on the treatment of MS, specifically links the use of DMF and/or MMF to the treatment of MS through Method 4, and describes 480 mg/day of DMF and/or MMF as an "effective dose" in the narrowest dosing range, connecting it to a known effective dose for treating MS. In other words, the '514 patent provides the blaze marks lacking in Nilsson.

IV. DEFENDANTS FAILED TO PROVE BY CLEAR AND CONVINCING EVIDENCE THAT THE INVENTION OF THE '514 PATENT IS NOT ENABLED

Defendants' enablement attack simply repeats their written description arguments, and thus fails for the reasons discussed above. (Def. Op. Br. at 17-18.)

"To prove that a claim is invalid for lack of enablement, a challenger must show by clear and convincing evidence that a person of ordinary skill in the art would not be able to practice the claimed invention without 'undue experimentation.'" *Alcon*, 745 F.3d at 1188 (quoting *In re Wands*, 858 F.2d 731, 736-37 (Fed. Cir. 1988)).[7] A patent "does not need to guarantee that the

[7] Undue experimentation is assessed under an analysis of the *Wands* factors, which include the: (1) quantity of experimentation necessary; (2) amount of direction or guidance presented; (3) presence or absence of working examples; (4) nature of the invention; (5) state of the art; (6) relative skill of those in the art; (7) predictability or unpredictability of the art; and (8) breadth of the claims. *Wands*, 858 F.2d at 737.

invention works for a claim to be enabled." *Id.* at 1189. Here, as discussed in detail above, the patent discloses the claimed method of treating MS with DMF and or MMF at a dose of 480 mg/day and further describes compositions that may be used to practice the claims including those disclosed in the '376 patent. (RFF 88, 91.) Example 1 in the '376 patent teaches preparation of "enteric-coated [DMF] microtablets in capsules." (RFF 94; DTX340 at 6:10-53), the same DMF formulation Biogen used in its Phase II study. (RFF 84, 94.) Skilled artisans could therefore make and use the claimed invention without undue experimentation. *See Alcon*, 745 F.3d at 1189 ("[T]he patents disclose exemplary compositions within the scope of the claims, detail how those example compositions are prepared . . . and provide step-by-step procedures for [practicing] the claimed invention."). Defendants' Drs. Yong and Lindsey did not consider this section of the specification in forming their opinions. (RFF 89; Yong 99:5-9; Lindsey 161:13-24.) Accordingly, Defendants have failed to prove by clear and convincing evidence that the asserted claims are not enabled.

V. DEFENDANTS FAILED TO PROVE BY CLEAR AND CONVINCING EVIDENCE THAT THE INVENTION OF THE '514 PATENT IS INVALID FOR DERIVATION

Credible testimony from multiple witnesses, corroborated by contemporaneous documents, established that Dr. O'Neill conceived of the claimed method of treating MS with 480 mg/day in late 2003 or early 2004. Faced with this evidence, Defendants concede that Dr. O'Neill "propose[d]" the 480 mg/day dose of DMF to treat MS at this time. (*See* Def. Op. Br. at 18-20.) Defendants nevertheless raise a series of contradictory arguments attempting to negate Dr. O'Neill's invention. They first contend that while Dr. O'Neill "propose[d]" the 480 mg/day dose, he somehow did not fully conceive of the invention, and that the FDA actually conceived of the invention over two years later and communicated it to Biogen, including to Dr. Lukashev. Defendants then offer the contradictory argument that the fact that "Dr. O'Neill allegedly conceived of the full invention in 2004, independent of Dr. Lukashev, shows there was no joint

inventorship and constitutes improper inventorship." (*Id.* at 20-21.) Defendants' conflicting arguments find no support in fact or law.

Derivation occurs when an individual "did not himself invent the subject matter sought to be patented." *Cumberland Pharms. Inc. v. Mylan Institutional LLC*, 846 F.3d 1213, 1217 (Fed. Cir. 2017). Derivation turns on a finding of a ***prior conception*** by a third party of the claimed subject matter and communication of the conception to the inventor. *Id.* at 1217-18 (citing *Price v. Symsek*, 988 F.2d 1187, 1190 (Fed. Cir. 1993)); *see Pfizer Inc. v. Teva Pharm. U.S.A., Inc.*, 882 F. Supp. 2d 643, 705-06 (D. Del. 2012) ("To prove derivation under § 102(f), the patent challenger must establish prior conception of the invention by another and communication of that conception to the patentee."). Here, Dr. O'Neill conceived of 480 mg/day DMF to treat MS by 2004, over two years before Biogen's August 2006 meeting with the FDA at which Defendants contend the FDA invented the 480 mg/day dose to treat MS. (RFF 7-8, 12-13, 17, 92-93, 95.) Because Defendants adduced no ***prior conception*** of the claimed subject matter, Defendants' argument fails as a matter of law. *Pfizer*, 882 F. Supp. 2d at 705-06.

Defendants' argument that Dr. O'Neill did not conceive of the claimed invention also fails. Conception "requires a definite and permanent, specific, settled idea, namely, the idea defined by the claim at issue." *Cumberland*, 846 F.3d at 1218. Derivation concerns first-in-time conception and communication of an invention. *See id.* By 2004, Dr. O'Neill had such a settled idea, as he testified to at trial. (RFF 7, 12-13, 93.) Corroborating documents and the consistent testimony of multiple, credible witnesses involved in the development of Tecfidera® confirm Dr. O'Neill's conception as presented in February 2004. (RFF 17.) To the extent Defendants argue (incorrectly) that Biogen "effectively abandoned" the idea to test 480 mg/day (Def. Op. Br. at 19), the argument is simply irrelevant to derivation.

Defendants' FDA conception arguments are also without merit. First, the FDA itself cannot be considered an inventor. "[I]ndividuals, not corporations, create inventions." *MBO Labs., Inc. v. Becton, Dickinson & Co.*, 602 F.3d 1306, 1309 n.1 (Fed. Cir. 2010); *see also Beech Aircraft Corp. v. EDO Corp.*, 990 F.2d 1237, 1248 (Fed. Cir. 1993). Defendants at most allege conception by "those at the FDA" but fail to identify any individual who supposedly conceived of a 480 mg/day dose. Identification of such a person is necessary for showing "prior conception" under § 102(f). Second, the undisputed evidence showed that Biogen had planned to test 480 mg/day long before its 2006 FDA meeting. (RFF 31, 34, 94.) During its August 2006 meeting with FDA, Biogen sought consensus on the highest dose it planned to test, 720 mg/day. (RFF 37.) Thus, discussion of any lower dose, including the planned 480 mg/day dose, was unnecessary. (RFF 37.) In 2006, Biogen finalized the Phase III protocols to test 480 mg/day and 720 mg/day and constructively reduced to practice the 480 mg/day dose by filing the patent application in February 2007. (RFF 21-22, 40.)

Defendants' arguments about the impropriety of Dr. Lukashev and Dr. O'Neill being co-inventors are also without merit. A specification may support more than one invention, *see* 35 U.S.C. § 121, and a patent properly lists all inventors, even those who did not contribute to every claim of the patent. 35 U.S.C. §116; *see also Vapor Point LLC v. Moorhead*, 832 F.3d 1343, 1348-49 (Fed. Cir. 2016) ("All inventors, even those who contribute to only one claim or one aspect of one claim of a patent, must be listed on that patent."); *Smithkline Diagnostics, Inc. v. Helena Labs. Corp.*, 859 F.2d 878, 888 (Fed. Cir. 1988) ("Inventors may apply for a patent jointly even though (1) they did not physically work together or at the same time, (2) each did not make the same type or amount of contribution, or (3) each did not make a contribution the subject matter of every claim of the patent.") (quoting 35 U.S.C. § 116); MPEP 2137.01. Dr. Lukashev, as the research scientist

on the BG-12 team studying mechanisms of action and related pre-clinical investigations, contributed to unasserted claims 17-19 of the '514 patent. (RFF 10, 97.) Dr. O'Neill served as the Medical Director and contributed to the asserted claims. (RFF 7, 97.) Inventors can be properly added at any time, even after a patent issues. 35 U.S.C. § 256. Moreover, the undisputed evidence showed that both inventors worked on Biogen's BG-12 MS team during the development of Tecfidera®. (RFF 11, 97.)[8] Accordingly, Defendants have failed to prove improper inventorship by clear and convincing evidence.

VI. DEFENDANTS FAILED TO PROVE BY CLEAR AND CONVINCING EVIDENCE THAT THE INVENTION OF THE '514 PATENT IS OBVIOUS

Under the law and as explained in Biogen's opening brief, Defendants burden to prove invalidity by clear and convincing evidence remains on them at all times. *See* Biogen Op. Br. at 3. As explained in detail below, Defendants have failed to meet their initial burden of establishing a *prima facie* case of obviousness. *See Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 291-92 (Fed. Cir. 1985) ("The presumption of validity is a procedural device that mandates that the party asserting invalidity bears the initial burden of establishing a *prima facie* case of obviousness under 35 U.S.C. § 103 . . . ."). Defendants have not met their burden of demonstrating "by clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." *Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009).

[8] Defendants' reliance on *Swanson v. Alza Corp.*, 2015 WL 1304436 (N.D. Cal. Mar. 20, 2015), is misplaced. Here, the evidence establishes that Dr. O'Neill contributed to the claimed 480 mg/day dose and therefore contributed the '514 patent claims. (RFF 7, 12, 17, 97.) Moreover, Dr. O'Neill and Dr. Lukashev both worked together on Biogen's BG-12 MS team, while in *Swanson* the plaintiff alleged that his conception occurred before ever meeting with and starting his consultancy for the defendant, "foreclos[ing] the possibility of any collaboration or open lines of communication with the [defendant] inventors." *Id.* at *12.

A. Dr. O'Neill's Own Work is Not Prior Art

Defendants' obviousness theories fail at the outset, because they rely primarily on references that are not prior art as to Dr. O'Neill's claimed methods. Specifically, the results of Dr. O'Neill's work reported in May 2006—in documents Defendants refer to as the Kappos Presentation 2006 (DTX329), Kappos Abstract 2006 (DTX327) and Biogen Press Release May 2006 (DTX441)—are not prior art, because an inventor's own work published less than a year before the priority date is not prior art under § 102(a). *In re Katz*, 687 F.2d 450, 454 (C.C.P.A. 1982) ("[O]ne's own work is not prior art under § 102(a) even though it has been disclosed to the public in a manner or form which otherwise would fall under § 102(a)"); *Mannesmann Demag Corp. v. Engineered Metal Prods. Co.*, 605 F. Supp. 1362, 1370 (D. Del. 1985), *aff'd*, 793 F.2d 1279 (1986) (finding a brochure not prior art under § 102(a) because it described the work and invention of the inventor). As Biogen's witnesses testified and the documents showed, Dr. O'Neill, the leader of Biogen's Phase II study, was "accountable for the design, execution, monitoring, data collection, data analysis and conclusions of the study." (O'Neill 527:25-528:2; RFF 99-100.) As such, the references in question reflect his work and are his actual work product. Indeed, Dr. O'Neill was the "[s]enior author" of the Kappos Presentation 2006 and also "prepared" the Kappos Abstract 2006. (O'Neill 530:5-6; RFF 24-28.)[9] The May 2006 press release reported select aspects of the study's results more fully reported in Kappos Presentation 2006 and Kappos Abstract 2006. (RFF 29-30.) Accordingly, these three references, all dated within a year of Biogen's priority date, are not prior art. *See Eli Lilly Co. v. Teva Pharms.*, 657 F. Supp. 2d 967,

[9] Defendants argue that Dr. Kappos "is accredited with drafting the clinical study protocol and statistical plan," (Def. Op. Br. at 23), but the article they rely on merely states that he was "***involved in*** drafting and amending study protocol and statistical analysis plan . . . ." (DTX451_0009) (emphasis added). Defendants presented no evidence that anyone other than Dr. O'Neill was the head of Biogen's Phase II study of DMF for MS and directed and supervised the other members of the study team.

1014 (S.D. Ind. 2009) (finding a publication not prior art under § 102(a) because the inventor, and not his coauthors, was the one primarily responsible for designing and conducting the clinical study). The facts here are readily distinguishable from the authority Defendants cite, *Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952 (Fed. Cir. 2014), where the disputed reference did not even list the inventor as a co-author and the inventor's testimony was "at best equivocal." *Id.* at 969.

B. A POSA Would Not Have Been Motivated To Administer 480 mg/day DMF To Treat MS with a Reasonable Expectation of Success

1. A POSA Would Have Been Motivated to Test A Dose Higher Than 720 mg/day

Even if the references that Defendants rely on reporting Biogen's Phase II results in May 2006 were prior art, which they are not, they would have motivated a POSA to test doses higher than 720 mg/day and not to pursue the claimed invention.[10] Only 720 mg/day, the highest tested dose, demonstrated statistically significant efficacy compared to placebo, and that dose exhibited "unimpressive, interferon like" efficacy. (D.I. 353 FF 28-35; RFF 98.) Thus, skilled artisans would have been motivated by these results to pursue doses higher than 720 mg/day, not the lower claimed dose of 480 mg/day. (RFF 107-08.) In fact, the investigators involved in the study at this time questioned "whether [Biogen] had dosed high enough." (RFF 113.) Defendants' Dr. Stobbe admitted that in February 2007 a POSA could not rule out that doses higher than 720 mg/day DMF would show greater efficacy in treating MS than reported. (RFF 109.)

The safety and tolerability data reported in Biogen's Phase II study results would not have dissuaded a POSA from pursuing doses higher than 720 mg/day. As Dr. Duddy explained, the

[10] As noted above, Biogen's experts and Defendants' expert Dr. Stobbe all agreed on the following definition for a POSA: a person having at least a medical degree with at least three years of training in neurology and at least three years of clinical experience in treating MS. (Duddy 375:2-9; Wynn 595:11-16; Stobbe 205:11-12, 206:4-23; RFF 56-58.) The Patent Office has agreed with this definition as well. D.I. 354-1 at 8.

"most important line for the person of ordinary skill looking at [the "Safety Conclusions" in the 2006 Phase II study presentation] is that the drug was perceived to be generally safe and well tolerated." (Duddy 429:4-10; RFF 108.) There is no suggestion in the study results of any tolerability problem or that patients could not tolerate the highest tested dose, 720 mg/day. (Duddy 429:4-10; RFF 110.) The additional reported data was consistent with the safety conclusions. (RFF 111.) As Defendants conceded, the Phase II "serious adverse events" are "a wash for this analysis. It doesn't point in one direction or another." (Closing 906:14-16; RFF 100-11.) The reported discontinuations similarly showed "an equal number at . . . 360 and 720, so there was no advantage moving from either direction." (Duddy 429:21-23; RFF 111.) The only remaining safety data—reporting the number of "adverse events"—simply provided incidence data, which does not indicate the relative severity of adverse events, and further showed "no ceiling of tolerability reached." (RFF 108, 110.) As Dr. Duddy concluded: "[e]verything would be telling me here with this drug you want to look beyond 720, try to get to the level of efficacy which as physicians and patients we want." (Duddy 430:20; 431:21-432:4; RFF 110.)

Defendants' argument that "[i]n view of the Joshi References and the Phase II study, a POSA would have been motivated to find the 'lowest effective dose of DMF,'" Def. Op. Br. at 24, is thus without merit. Defendants place undue emphasis on side effects and disregard the actual Phase II study results and conclusions demonstrating that the severity of side effects was comparable at all doses and that all doses were all "safe and well tolerated." (RFF 103-04.) In light of these facts, a skilled artisan would have had no motivation to explore DMF doses below the safe but lackluster 720 mg/day dose and thus the general teachings of ICH Guidelines and Richter 2003 relating to dose optimization are not relevant to the obviousness analysis here. (RFF 106.)

Defendants relatedly contend that a skilled artisan would not seek to explore doses higher than 720 mg/day because doing so allegedly "would require either more frequent daily administration (more than 3-times daily) and/or larger individual doses," increasing the likelihood of dose-related side effects. (Def. Op. Br. at 27-28.) This argument ignores the safety results reported in Biogen's Phase II study and further ignores other art teaching safe administration of nearly 1,300 mg of fumarates daily, including individual doses of 430 mg of fumarates. (RFF 104.) Thus, the art taken as a whole does not indicate any obstacle in pursuing doses greater than 720 mg/day. Defendants also improperly point to internal safety data in confidential communications between Biogen and the FDA, but this information was unavailable to skilled artisans and cannot inform an obviousness analysis. (Def. Op. Br. at 28; RFF 112.) Defendants' reliance on *In re Copaxone Consolidated Cases*, 906 F.3d 1013 (Fed. Cir. 2018), is misplaced. In *Copaxone*, the cited non-prior art information was consistent with actual prior art teachings that were properly part of an obviousness analysis; thus, the Federal Circuit did not fault the trial court's reliance on non-prior art that was "merely confirmation of how a POSITA would understand" the prior art. *Id.* at 1030. Here, the non-prior art information did not reflect the teaching of any of the reported Phase II results.

2. The Phase II Results Did Not Report A Range of Effective Doses

The Phase II results did not report, let alone supposedly narrow, an effective dose range to treat MS. Defendants argue that, based on the limited Phase II study details reported by January 2006,[11] a POSA would have reasonably expected an effective DMF dose "range between 120-720 mg/day." (Def. Op. Br. at 25.) Defendants then contend a POSA would seek to optimize doses in this range. This argument is contradicted by the evidence. The January 2006 document (DTX319)

[11] Defendants offered no evidence that DTX319 was in fact publicly available on a particular date and was therefore prior art under Section 102(b).

that Defendants rely on merely states that the Phase II study "met its primary endpoint" without identifying the tested doses or the magnitude of the effect seen at any dose. (Duddy 435:17-436:23; RFF 114.) As the Patent Office recently held, DTX319 "fails to establish any effective dose range for DMF . . . ." (D.I. 354-1 at 17.) Defendants' reliance on case law regarding "disclosed ranges" is thus misplaced. (*See* Def. Op. Br. at 25.)

Simply put, the Phase II results did not "add[] more dose-response information of DMF to treat MS." (Def. Op. Br. at 26.) Only a single dose—the highest tested dose of 720 mg/day—demonstrated statistically significant efficacy compared to placebo. (RFF 114.) And a single dose cannot establish an effective range. As Dr. Stobbe admitted, a POSA would need "at least two" but "[i]deally even more" data points to determine if or where a plateau in efficacy existed in a dose-response curve. (Stobbe 248:10-17; *see also* Duddy 432:18-433:2; RFF 116.) Dr. Stobbe thus conceded that the dose-response relationship in Biogen's Phase II study was not adequately defined. (RFF 116.) Accordingly, the Phase II results did not report a range of effective DMF doses to treat MS. (RFF 117; *see also* Duddy 470:1-9 ("[T]here is no effective range of dimethyl fumarate treatment" in the Phase II trial).)[12]

Finally, Defendants cite Nieboer 1990 and Nilsson to support their invalidity arguments. Nieboer 1990, however, relates to the treatment of psoriasis, not MS, and all parties agree that dosing for one disease (such as psoriasis) does not inform dosing for another disease (such as MS). (RFF 102-04.) Nilsson suffers from this same deficiency, among others. (RFF 102-04, 118-24.) Nilsson discloses no specific dose to treat any specific disease, instead disclosing a long list of

[12] Any optimization would also not be limited to 120 mg dosing increments as Defendants incorrectly contend. The Joshi References, to which Defendants repeatedly point, do not disclose any daily dosage amount, but do describe dosage forms varying from 10 to 300 mg, "illustrating that there is no reason why you would have to think in multiples of 120." (Duddy 456:3-8; RFF 101, 115.)

wide-ranging conditions with no focus on MS, indiscriminate possible doses in a scale-up treatment schedule, and a broad scope of fumaric acid esters. (RFF 102-04, 118-24.) This broad disclosure does not teach or suggest the claimed invention. *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988) ("One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to depreciate the claimed invention.").

Accordingly, for these reasons and those explained in Biogen's opening brief (D.I. 352), in which Biogen offered significant evidence of unexpected results, which has been confirmed by the Patent Office in its recent IPR decision on the '514 patent, Defendants have not met their heavy burden to prove obviousness.

VII. DEFENDANTS FAILED TO PROVE BY CLEAR AND CONVINCING EVIDENCE THAT THE INVENTION OF THE '514 PATENT IS ANTICIPATED

Defendants' anticipation theory based on Nilsson is foreclosed as a matter of law because the Federal Circuit has held that Nilsson does not disclose, and thus cannot anticipate, the 480 mg/day DMF dose to treat MS. *Biogen*, 749 Fed. Appx. at 977; 35 U.S.C. § 102 ("A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.").

Nilsson cannot anticipate the claimed invention of the '514 patent because it would require a POSA to arbitrarily pick and choose from a long list of wide-ranging disease conditions, indiscriminate possible doses and broad scope of fumaric acid esters. *See Biogen*, 749 Fed. Appx. at 975-77. (RFF 118, 124.) Such "picking and choosing . . . has no place in the making of a 102, anticipation rejection." *In re Arkley*, 455 F.2d 586, 587 (C.C.P.A. 1972). In fact, Defendants do not even attempt to offer the required claim-by-claim analysis for this defense. *See Elan Corp., PLC v. Andrx Pharms., Inc.*, 366 F.3d 1336, 1342 (Fed. Cir. 2004).

More specifically, Nilsson is primarily directed to controlled release compositions that allegedly reduce GI side effects associated with the *psoriasis* treatment Fumaderm®. (RFF 119.) Nilsson discloses a list of more than twenty untested diseases and conditions, and MS is mentioned in this list and only once in the entire specification. (RFF 119.) No disease or condition in this list, much less MS specifically, is associated with any particular dose of any particular active agent. (RFF 119.) As to dose, Nilsson discloses a nine-week up-titration chart that is *essentially identical* to the up-titration schedule known and used for the treatment of psoriasis with Fumaderm®. (RFF 120.) Although 480 mg per day is administered for week seven of the nine-week titration schedule, this amount, at best, is merely a *one-week interim dose* within an upward titration to achieve a 720 mg per day dose for treating *psoriasis*. Nilsson also lists a ladder of possible daily doses, with no regard or information as to whether they would actually serve to treat any particular disease or condition. (RFF 122.) The paragraph is nothing more than an extension of the up-titration chart's concept, i.e., the recognition that each individual Fumaderm® tablet contains certain fumarate salts and 120 mg of DMF, leading to a ladder of equally spaced multiples from 240 mg to 1080 mg. (RFF 122.) Nilsson also fails to connect any amount on this ladder to DMF or MMF. It merely refers to "active substance," which could be any number of fumaric acid esters selected from di-(C_1-C_5)alkylesters and mono-(C_1-C_5)alkylesters referred to in the Nilsson specification. (RFF 123.) To arrive at the claimed invention of Biogen's '514 patent, a POSA would be required to pick and choose from a slew of possibilities for each of the three variables.

VIII. CONCLUSION

For the reasons explained herein and in Biogen's opening brief, Defendants have not carried their heavy burden of proving by clear and convincing evidence that the asserted '514 patent claims are invalid.

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